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Pharmaceutical formulation for nasal administration for treating diabetes
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Number of Countries: 084 Number of Patents: 007
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CN 1235846	A	19991124	CN 98108852	A	19980520	200014	
AU 9930550	A	19991206	AU 9930550	A	19990401	200019	
EP 1079801	A1	20010307	EP 99912088	A	19990401	200114	
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JP 2002515416	W	20020528	WO 99JP1704	A	19990401	200238	
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JP 2002193830	A	20020710	JP 98313934	A	19981019	200260	
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Abstract (Basic): **WO 9959543** A1

NOVELTY - A pharmaceutical formulation for nasal administration comprises:

(1) a polypeptide;

(2) taurine, an ester of taurine with a 1-6C alcohol, a base metal salt of taurine, hyaluronic acid and/or a base metal salt of hyaluronic acid; and

(3) at least one additive.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a method for producing a pharmaceutical formulation for nasal administration which contains at least one polypeptide, comprising:

(a) adding an adequate amount of distilled water to taurine, an ester of taurine with a 1-6C alcohol, a base metal salt of taurine,

hyaluronic acid and/or a base metal salt of hyaluronic acid and an optional additive to form a solution of the ingredients;

(b) adjusting the pH of the solution formed by dissolving the compounds; and

(c) adding a polypeptide to the solution and dissolving the polypeptide.

ACTIVITY - Antidiabetic.

An insulin-containing pharmaceutical formulation for nasal administration comprised e.g. insulin (20000 IU), taurine (2g), hyaluronic acid (1g), 0.1N HCl or 0.1N NaOH (adequate amount), nipagin A (p-hydroxy benzoic acid ethyl ester) (0.03g) and distilled water (to 100ml). The effect of the formulation was examined with respect to the blood sugar level in alloxan diabetes of rats caused by administration of alloxan. 4 hours after administration of 10 U/kg of the formulation, the decrease in blood sugar levels was 56.3 mg/dl.

USE - The pharmaceutical formulation can be used for the treatment of type I and type II diabetes.

ADVANTAGE - No adverse effects such as irritation were observed and hence the present formulation may be administered through nasal mucosa.

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Derwent Class: B07

International Patent Class (Main): A61K-009/00; A61K-038/00; A61K-038/22

International Patent Class (Additional): A61K-009/08; A61K-038/28; A61K-047/20; A61K-047/36; A61K-047/48

A PHARMACEUTICAL FORMULATION FOR NASAL ADMINISTRATION

Patent number: WO9959543
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Inventor: MA XIN FANG (CN)
Applicant: MA XIN FANG (CN); CHARNA CHEMICALS LTD (CN); HIGHCHEM COMPANY LTD (JP)
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WO9843664
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Abstract of **WO9959543**

This invention discloses a pharmaceutical formulation for nasal administration which contains a pharmaceutically active polypeptide and a method for producing the pharmaceutical formulation. The pharmaceutical formulation comprises: (1) a pharmaceutically active polypeptide, (2) at least one compound selected from the group consisting of taurine, an ester thereof with C1 SIMILAR 6 alcohol, a base metal salt of taurine, hyaluronic acid and a base metal salt of hyaluronic acid, and (3) at least one pharmacologically acceptable additive. It exhibited excellent pharmaceutical activity. No adverse effects such as irritation were observed and hence, the present pharmaceutical formulation may suitably be administrated through nasal mucosa.

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(54) Title: A PHARMACEUTICAL FORMULATION FOR NASAL ADMINISTRATION

(57) Abstract

This invention discloses a pharmaceutical formulation for nasal administration which contains a pharmaceutically active polypeptide and a method for producing the pharmaceutical formulation. The pharmaceutical formulation comprises: (1) a pharmaceutically active polypeptide, (2) at least one compound selected from the group consisting of taurine, an ester thereof with C1~6 alcohol, a base metal salt of taurine, hyaluronic acid and a base metal salt of hyaluronic acid, and (3) at least one pharmacologically acceptable additive. It exhibited excellent pharmaceutical activity. No adverse effects such as irritation were observed and hence, the present pharmaceutical formulation may suitably be administrated through nasal mucosa.

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DESCRIPTION

A pharmaceutical formulation for nasal administration

TECHNICAL FIELD

The present invention relates to a pharmaceutical formulation for nasal administration containing a pharmaceutically active polypeptide, and particularly relates to a pharmaceutical formulation for nasal administration that comprises at least one compound selected from the group consisting of taurine, an ester thereof with C1~6 alcohol, a base metal salt of taurine, hyaluronic acid and a base metal salt of hyaluronic acid. These compounds are used as absorbefacients for the pharmaceutical formulation of the present invention. The pharmaceutical formulation of the present invention may be dosed through nasal mucosa. The present invention also relates to a method for producing the pharmaceutical formulation.

BACKGROUND ART

A powder composition for nasal administration including a physiologically active peptide with a hyaluronic acid butyrene glycol ester as a carrier is disclosed in Japanese Patent Publication (laid-open) No. 6-199681. A pharmaceutical composition for administration through nasal mucosa, with preferably a pH of about 4, containing a peptide hormone and hyaluronic acid or its salt is disclosed in Japanese Patent Publication (laid-open) No. 3-246233. A microsphere formed comprising a physiologically active peptide that is surrounded by hyaluronic acid esters or which is adsorbed on hyaluronic acid esters is disclosed in Japanese Patent Publication (laid-open) No. 7-179363. A pharmaceutical formulation with improved drug delivery comprising a physiologically active peptide, hyaluronic acid or a non-toxic salt of these compounds, and polymer substance is disclosed in Japanese Patent Publication (laid-open) No. 5-97694. A pharmaceutical formulation for administration through the lung that comprises peptide type drugs and hyaluronic acid is disclosed in Japanese Patent Publication (laid-open) No. 9-309843. A pharmaceutical formulation with sustained physiological activity comprising hyaluronic acid or its non-toxic salts is disclosed in Japanese Patent Publication

(laid-open) No. 2-213. A powder pharmaceutical formulation for nasal administration that contains a granulocyte colony stimulating factor, saccharides, hyaluronic acid or its salt is disclosed in Japanese Patent Publidcation (laid-open) No. 8-198772. An eye drop containing insulin and hyaluronic acid or its salt as a thickening agent is disclosed in Japanese Patent Publication (laid-open) No.1-294633. An aqueous pharmaceutical composition with sustained pharmaceutical activity that contains a pharmaceutically active peptide, water soluble hyaluronic acid, and a water soluble protein which does not exhibit pharmaceutical activity is disclosed in Japanese Patent Publication (laid-open) No. 5-186362. A peptide composition having a physiologically active peptide homogeneously dispersed in a carrier hyaluronic acid so that is it adhesively bound to the carrier is disclosed in Japanese Patent Publication (laid-open) No. 7-118170. A super-absorbent drug for administration through vagina that contains the absorbefacient taurine in a bioactive polypeptide is disclosed in Japanese Patent Publication (laid–open) No. 3-99021. In Chinese Patent Application No. 95119260.4, an absorbefacient for absorption of peptide containing pharmaceuticals through mucosae is disclosed. The absorbefacients disclosed in the above Chinese application include azone, saponins, glycyrrhizionic acid, and esters, salts of these compounds, glycyrrhetinic acid and a sodium salt of glycyrrhetinic acid, dihydroxymorintannic acid and its derivatives, and carboxylic acid esters of these compounds. However, the only formulation example disclosed in the above Chinese Patent Application is a sublingual tablet containing such absorbefacients. In Chinese Patent Application No. 88106763.6, a pharmaceutical formulation for administaration through mucosae is disclosed. The absorbefacients contained in the formulation are monosaccarides such as D-erythrose, D-ribose, D-ribulose, D-xylose, D-arabinose, D-mannose, L-sorbose, D-sedumtheptulose, or monosacarides such as α -cyclodexstrin, β -cyclodexstrin, γ -cyclodexstrin, and cyclodexstrin having side chains.

Polypeptide compounds are easily degraded with enzymes in the human stomach and intestines and are easily metabolized in the human lever. Therefore, polypeptide compounds are difficult to give their intrinsic pharmaceutical effects in a patient's body. Thus, polypeptide compounds are generally administered as various injectiones such as hypodermic injections, intramuscular injections, and intravenous injections. However, the patient experiences pain and irritation such as, for example, injury and necrosis of his/her muscle tissue during long-term polypeptide administration of the injections and there is a potential for infections caused by injection due to communicable diseases. The patient

also experiences various inconveniences such as the need to receive regular outpatient treatment. For these reasons, extensive studies have recently been made to administer the polypeptide compounds through mucosae such as the nasal mucosa, no polypeptide containing pharmaceutical formulations for administration through the nasal mucosa have not yet been commercially available.

Therefore, polypeptide containing pharmaceutical formulations for administration through nasal mucosa are highly desired and their development has been waited for a long time.

An object of the present invention is to provide a pharmaceutical formulation for nasal administration containing a pharmaceutically active polypeptide and also to provide a method for producing thereof.

DISCLOSUE OF INVENTION

The inventor has found a novel pharmaceutical formulation suitable for nasal administration and succeeded in accomplishing the present invention as the result of the study to solve the above problems. The novel pharmaceutical formulation containing a pharmaceutically active polypeptide exhibits high pharmaceutical activity as high as the pharmaceutical activity obtained in the administration through injection and does not irritate patients.

According to the present invention, the pharmaceutical formulation for nasal administration comprises (1) a pharmaceutically active polypeptide, (2) at least one compound selected from the group consisting of taurine, an ester thereof with C1～6 alcohol, an base metal salt of taurine, hyaluronic acid and a base metal salt of hyaluronic acid, and (3) at least one pharmacologically acceptable additive.

Further according to the present invention, the pharmaceutical formulation for nasal administration preferably comprises (1) a pharmaceutically active polypeptide, (2) at least one compound selected from the group consisting of taurine, an ester thereof with C1～6 alcohol, a base metal salt of taurine, (3) at least one compound selected from hyaluronic acid and a base metal salt of hyaluronic acid, and (4) at least one pharmacologically acceptable additive.

Further according to the present invention, the pharmaceutical formulation for nasal administration more preferably comprises (1) a pharmaceutically active polypeptide, (2) taurine and hyaluronic acid, and (3) at least one pharmacologically acceptable additive.

Further according to the present invention, the pharmaceutical formulation may comprises at least one compound selected from the group consisting of taurine, an ester thereof with C1~6 alcohol, a base metal salt of taurine, hyaluronic acid, a base metal salt of hyaluronic acid and a mixture thereof or a carrier for the pharmaceutically active polypeptide for administration through the nasal mucosa.

In accordance with the present invention, a method for producing a pharmaceutical formulation is also provided. The method for producing a pharmaceutical formulation for nasal administration containing of at least one pharmaceutically active polypeptide comprises the steps of;

adding an adequate amount of distilled water to a compound selected from the group consisting of taurine, an ester thereof with C1~6 alcohol, a base metal salt of taurine, hyaluronic acid, a base metal salt of the hyaluronic acid, a mixture thereof, and an optional additive to form a solution of the ingredients;

adjusting the pH of the solution formed by dissolving the compounds; and

adding a pharmaceutically active polypeptide to the solution and dissolving the pharmaceutically active polypeptide.

Further according to the present invention, the method for producing the pharmaceutical formulation may further include the steps of;

filtering the solution for sterilization thereof; and

filling a bottle with the filtrate.

BEST MODE FOR CARRYING OUT THE INVENTION

In the present invention, examples of the pharmaceutically active polypeptide include natural insulin obtained from cow and pig or synthetic insulin, calcitonin, hirudin, glucagon, angiotensin,

lactation hormone, growth hormone, thyroid-stimulating hormone (THS) or thyrotropin, adrenocorticotropin, and inerferon, and mixtures thereof.

In a preferred embodiment of the present invention, a pharmaceutical formulation to be administered through the nasal mucosa for treatment of diabetes is provided. The pharmaceutical formulation of the preferred embodiment containes insulin as the above pharmaceutically active polypeptide.

The base metal salt of taurine is used as one of the absorbefacients which is contained in the pharmaceutical formulation for nasal administration according to the present invention. Exemplary base metal salts may include sodium salts of taurine and potassium salts of taurine, and the like. The base metal salt of hyaluronic acid is used as one of the absorbefacients which is contained in the pharmaceutical formulation for nasal administration according to the present invention. Exemplary of base metal salts may include sodium salts of hyaluronic acid and potassium salts of hyaluronic acid, and the like.

Insulin is one of the effective ingredients of the pharmaceutical formulation for nasal administration of the present invention and examples may include natural insulin obtained from cow and pig, synthetic insulin and insulin produced by a recombinant DNA technique.

Diabetes which is to be treated with the insulin-containing pharmaceutical formulation for nasal administration of the present invention may be type I diabetes or type II diabetes.

The pharmaceutical formulation for nasal administration of the present invention may be preferably formulated as a liquid drop type drug or a spray type drug. The pharmaceutical formulation for nasal administration of the present invention which may be provided either as a liquid drop type drug or as a spray type drug may be dosed, for example, through the nasal mucosa to a human.

The pharmaceutically active polypeptide containing pharmaceutical formulation of the present invention may possibly formulated from the pharmaceutically active polypeptide together with an

absorbefacient and/or a carrier. However, the inventor has found that significant therapeutic effect is obtained when the pharmaceutical formulation for nasal administration includes simultaneously the pharmaceutically active polypeptide, absorbefacient taurine or a derivative thereof and carrier hyaluronic acid or a derivative thereof.

The pharmaceutically active polypeptide containing pharmaceutical formulation for nasal administratrion of the present invention may preferably contain 0.01～20 w/v% of at least one absorbefacient compound selected from taurine, its ester with C1～6 alcohol, and its base metal salt and at least one carrier compond selected from 0.01～10 w/v% of at least one compound selected from hyaluronic acid and its base metal salts, or a mixture thereof.

In the present invention, an aqueous solution containing a pharmaceutically active polypeptide or a the pharmaceutical formulation for nasal administration, pH may generally range from 6 to 8, more preferably range from 6.5 to 7.5.

The pharmaceutical formulation for nasal administration of the present invention which contains a pharmaceutically active polypeptide may be produced, for example, according to the following steps;

adding an adequate amount of distilled water to a compound selected from the group consisting of taurine, its ester with C1～6 alcohol, its base metal salt, hyaluronic acid, its base metal salt of the hyaluronic acid, a mixture thereof, and an optional additive such as, for example, a preserving agent Nipagin A (p-hydroxybenzoic acid ethyl ester) to form a solution of the ingredients;

adjusting the pH of the solution to between 6.5 and 7.5, more preferably to about 7.0, with 0.1 N HCl or 0.1N NaOH after dissolving the compounds by heating the mixture; and

adding a pharmaceutically active polypeptide such as insulin to the above solution and dissolving the pharmaceutically active polypeptide.

The above process may optionally includes the steps of;

filtering the above solution for sterilization thereof; and

filling a bottle with the filtrate. The bottle may be specially produced for this purpose.

According to the present invention, the dose of the pharmaceutically active polypeptide

containing pharmaceutical formulation for administration through the nasal mucosa may vary with patient's age, body weight, health condition, the severity of the disease, drugs to be simultaneously administered, their kinds, and the kind of the pharmaceutically active polypeptide. Generally, the dose of the pharmaceutical formulation for nasal administration of the present invention which contains a pharmaceutically active polypeptide may be determined according to known doses of the pharmaceutically active polypeptide used.

EXAMPLES

Embodiments of the present invention are further explained by the following particular examples. These examples are described only for explanation rather than for limiting the scope of the present invention

Example 1

Production of pharmaceutical formulation for nasal administration:

Formulation:

Ingredients	Amount
Insulin	20000 IU
Taurine	2g
0.1N HCl or 0.1N NaOH	adequate amount
Nipagin A (p-hydroxy benzoic acid ethyl ester)	0.03g
Distilled water	make to 100ml

To the mixture of taurine and Nipagin A, an adequate amount of distilled water was added, then the mixture was heated to dissolve the ingredients. After dissolving the ingredients, the solution was adjusted to pH=7 with 0.1N HCl or 0.1N NaOH. After that, insulin was added to the solution.

After insulin was dissolved, the solution was filtered for sterilization thereof. The resulting filtrate was charged into a specially made sterilized bottle.

Example 2

Production of pharmaceutical formulation for nasal administration:

Formulation:

Ingredients	Amount
Insulin	20000 IU
Hyaluronic acid	0.5g
0.1N HCl or 0.1N NaOH	adequate amount
Nipagin A (p-hydroxy benzoic acid ethyl ester)	0.03g
Distilled water	make to 100ml

To the mixture of hyaluronic acid and Nipagin A, an adequate amount of distilled water was added, then the mixture was heated to dissolve the ingredients. After dissolving the ingredients, the solution was adjusted to pH=7 with 0.1N HCl or 0.1N NaOH. After that, insulin was added to the solution. After insulin was dissolved, the solution was filtered for sterilization thereof. The resulting filtrate was charged into a specially made sterilized bottle.

Example 3

Production of pharmaceutical formulation for nasal administration:

Formulation:

Ingredients	Amount
Insulin	20000 IU
Taurine	2g
Hyaluronic acid	1g
0.1N HCl or 0.1N NaOH	adequate amount
Nipagin A (p-hydroxy benzoic acid ethyl ester)	0.03g
Distilled water	make to 100ml

To the mixture of taurine, hyaluronic acid and Nipagin A, an adequate amount of distilled water was added, then the mixture was heated to dissolve the ingredients. After dissolving the ingredients, the solution was adjusted to pH=7 with 0.1N HCl or 0.1N NaOH. After that, insulin was added to the solution. After insulin was dissolved, the solution was filtered forsterilization thereof. The resulting filtrate was charged into an specially made sterilized bottle.

Example 4

The insulin-containing pharmaceutical formulation for nasal administration was formulated as a collunarium or a nasal drop type drug according to the present invention. The pharmaceutical formulation was examined with respect to the blood suger level in alloxan diabetes of rats caused by administration by alloxan injections. Control experiments were simultaneously conducted under the same conditions.

Materials:

Animal: Animals used were Wistar rats, male, body weight between 200g and 220g, which were purchased from Chinese Military Medical Animal Center with certificate number: Beijing Testing Animal Control Number (1994) No. 052:

The pharmaceutical formulation containing insulin according to the present invention: three different dose levels of 10 IU/kg, 5 IU/kg, 2.5 IU/kg were used in the examples.

Reagent and Instruments:

Alloxan: Commercially available alloxan made in Hong Kong, Lot No. FL0610021153:
UV-VIS spectrophotometer: Commercially available UV-VIS spectrophotometer made in Japan:

Experimental Procedure:

Healthy rats were selected from the above Wistar rats and fasted for 24 hr, except that they were allowed to drink water ad libitum. After fasting, a solution of 40 mg/kg of an alloxan salt was intravenously injected to each rat. After 36 hr from the injection of alloxan, the rats were fasted for 12 hr, except that they were allowed to drink water ad libitum. After additional 12hr, an experiment was started. In the experiment, the sugar level of collected blood was measured. The blood was collected after injecting an anesthetic to the rats. The anesthetic and its dose were sodium pentobarbital and 30 mg/kg per rat, respectively. An experiment was also conducted using a blank control group, a model group, and a treated group. The blank control group was a group in which the rats were not administered alloxan by injection while the rats in the other two groups were injected alloxan. The rats in the blank control group and the model group were administered a control pharmaceutical formulation which had the same composition as the formulation of the present invention except that they contained no insulin. The administration to these two groups was made by dropping the control pharmaceutical formulation to their nostrils. The control pharmaceutical formulation was dropped in 10 μl/100g. For rats in the treated group, the pharmaceutical formulations for nasal administration according to the present invention containing10 IU insulin/kg, 5 IU insulin/kg, or 2.5 IU insulin/kg were dosed by

dropping into their nostrils with the same amount of the pharmaceutical formulation (10 μl/100g) as for the blank control group and the model group. Blood was collected from the rats in each group after 1 hr, 2 hr, 3 hr, and 4 hr from the administration of the formulation according to the present invention. The result is shown in Table 1.

According to the data in Table 1, the insulin-containing pharmaceutical formulation according to the present invention is easily absorbed by the nasal mucosa and exhibits significant blood sugar level lowering effects.

INDUSTRIAL APPLICABILITY

The pharmaceutical formulation for nasal administration which contains a pharmaceutically active polypeptide according to the present invention exhibited excellent pharmaceutical activity. No adverse effects such as irritation on the nasal mucosa were observed. Therefore, it is concluded that the pharmaceutical formulation according to the present invention is an excellent pharmaceutical formulation for administration through nasal mucosa.

Table 1: Pharmaceutical effects of insulin-containing nasal drop drugs on the alloxan induced high blood sugar levels of the Wistar rats when they were administered through nasal mucosa

Time after Administ -ration	Group	Dose	Number of rats per group	Percentage of rats with lowered blood sugar level (%)	Decrease in blood sugar level (mg/dl)	Decrease in blood sugar level (%)
1 hr	Blank group	10 μl/100g	10	60	5.9±3.1	8.5±5.1
	Model group	10 μl/100g	10	60	27.1±16.9	11.3±8.7
	Treated group	10 IU/kg	10	100	53.3±17.5	18.8±7.3
	Treated group	5 IU/kg	10	100	46.0±20.7	17.1±7.8
	Treated group	2.5 IU/kg	10	100	36.7±17.0	13.2±6.3
2 hrs	Blank group	10 μl/100g	10	60	8.1±4.6	11.0±6.3
	Model group	10 μl/100g	10	30	6.5±5.5	1.9±1.6
	Treated group	10 IU/kg	10	100	89.2±44.2	29.6±10.9
	Treated group	5 IU/kg	10	100	59.3±32.0	21.4±10.0
	Treated group	2.5 IU/kg	10	100	48.6±37.6	16.8±11.2
3 hrs	Blank group	10 μl/100g	10	30	5.1±2.1	7.2±3.0
	Model group	10 μl/100g	10	20	9.8±9.7	2.6±1.8
	Treated group	10 IU/kg	10	100	75.6±51.8	24.3±13.9
	Treated group	5 IU/kg	10	90	46.1±22.6	16.6±6.8
	Treated group	2.5 IU/kg	10	80	43.8±35.9	14.9±11.6
4 hrs	Blank group	10 μl/100g	10	0	0	0
	Model group	10 μl/100g	10	0	0	0
	Treated group	10 IU/kg	10	100	56.3±53.6	16.8±15.9
	Treated group	5 IU/kg	10	80	19.3±10.8	6.8±3.5
	Treated group	2.5 IU/kg	10	80	31.2±29.8	10.4±9.3

IU: International Unit

While the present invention has been explained by referring to specific examples, it is possible for a person skilled in the art to make variations and modifications of the embodiments described above without departing from the scope of the present invention. The scope of the present invention is limited only by the appended claims and not by the examples described above.

I claim;

CLAIMS

1. A pharmaceutical formulation for nasal administration comprising (1) a pharmaceutically acitive polypeptide, (2) at least one compound selected from the group consisting of taurine, an ester thereof with C1～6 alcohol, a base metal salt of taurine, hyaluronic acid and a base metal salt of hyaluronic acid, and (3) at least one pharmacologically acceptable additive.

2. The pharmaceutical formulation for nasal administration according to claim 1, which comprises (1) a pharmaceutically active polypeptide, (2) at least one compound selected from the group consisting of taurine, an ester thereof with C1～6 alcohol, a base metal salt of taurine, (3) at least one compound selected from hyaluronic acid and a base metal salt of hyaluronic acid, and (4) at least one pharmacologically acceptable additive.

3. A pharmaceutical formulation for nasal administration, which comprises (1) a pharmaceutically active polypeptide, (2) taurine and hyaluronic acid, and (3) at least one pharmacologically acceptable additive.

4. The pharmaceutical formulation for nasal administration according to claim 1, 2 or 3, wherein the pharmaceutically active polypeptide is selected from the group consisting of insulin, calcitonin, hirudin, glucagon, angiotensin, a lactation hormone, a growth hormone, a thyroid-stimulating hormone or thyrotropin, adrenocorticotropin, and inerferon.

5. The pharmaceutical formulation for nasal administration according to the claim 4, wherein the pharmaceutical active polypeptide is insulin.

6. The pharmaceutical formulation for nasal administration according to any one of the preceding claims, wherein the pharmaceutical formulation is a drop type formulation or a spray type formulation.

7. The pharmaceutical formulation for nasal administration according to any one of the preceding claims, which comprises 0.01～20 w/v% of at least one compound selected from the group consisting

of taurine, an ester thereof with C1～6 alcohol, and a base metal salt of taurine.

8. The pharmaceutical formulation for nasal administration according to any one of the preceding claims, which comprises 0.01～10 w/v% of at least one compound selected from the group consisting of hyaluronic acid and a base metal salt of hyaluronic acid.

9. The pharmaceutical formulation for nasal administration according to any one of the preceding claims, which comprises 0.01～20 w/v% of at least one compound selected from the group consisting of taurine, an ester thereof with C1～6 alcohol and a base metal salt of taurine and 0.01～10 w/v% of at least one compound selected from hyaluronic acid and a base metal salt of hyaluronic acid.

10. The pharmaceutical formulation for nasal administration according to any one of the claims, wherein the base metal salt is a sodium or potassium salt.

11. The pharmaceutical formulation for nasal administration according to any one of the preceding claims, wherein the pharmacologically acceptable additive is at least one compound selected form the group consisting of a preserving agent and an excipient.

12. The pharmaceutical formulation for nasal administration according to claim 11, wherein the pharmacologically acceptable additives contain an excipient and a preserving agent.

13. The pharmaceutical formulation for nasal administration according to claim 11 or 12, wherein the excipient is water.

14. The pharmaceutical formulation for nasal administration according to claim 11, 12 or 13 wherein the preserving agent is p-hydroxybenzoic acid ethyl ester.

15. The pharmaceutical formulation for nasal administration according to any one of the claims, wherein the pH of the formulation ranges from 6 to 8.

16. The pharmaceutical formulation for nasal administration according to claim 15, wherein the pH of the formulation ranges from 6.5 to 7.5.

17. A pharmaceutical formulation for nasal administration, which is used for therapeutics for diabetes, comprising (1) insulin, (2) at least one compound selected from the group consisting of taurine, an ester thereof with C1～6 alcohol, a base metal salt of taurine, hyaluronic acid and a base metal salt of hyaluronic acid, and (3) at least one pharmacologically acceptable additive.

18. The pharmaceutical formulation for nasal administration according to claim 17, which is used for therapeutics for diabetes, comprising (1) insulin, (2) at least one absorbefacient compound selected from the group consisting of taurine, an ester thereof with C1～6 alcohol, a base metal salt of taurine and, and (3) at least one carrier compound selected from hyaluronic acid and a base metal salt of hyaluronic acid, and (4) at least one pharmacologically acceptable additive.

19. A pharmaceutical formulation for nasal administration, which is used for therapeutics for diabetes, comprising (1) insulin, (2) taurine and hyaluronic acid, and (3) at least one pharmacologically acceptable additive.

20. The pharmaceutical formulation for nasal administration according to claim 17, 18 or 19, which is a drop type formulation or a spray type formulation.

21. The pharmaceutical formulation for nasal administration according to claim 17, 18,19 or 20, wherein the insulin is obtained from cow or pig or synthetic insulin.

22. The pharmaceutical formulation for nasal administration according to any one of the claims from 17 to 21, wherein the diabetes is of type I diabetes or type II diabetes.

23. The pharmaceutical formulation for nasal administration according to any one of the claims from 17 to 22, which contains 0.01～20 w/v% of at least one compound selected from the group consisting of taurine, an ester thereof with C1～6 alcohol, and a base metal salt of taurine.

24. The pharmaceutical formulation for nasal administration according to any one of the claims from 17 to 23, which contains 0.01～10 w/v% of at least one compound selected from the group consisting of hyaluronic acid and a base metal salt of hyaluronic acid.

25. The pharmaceutical formulation for nasal administration according to any one of the claims from 17 to 24, which contains 0.01～20 w/v% of at least one compound selected from the group consisting of taurine, an ester thereof with C1～6 alcohol, and a base metal salt of taurine and 0.01～10 w/v% of at least one compound selected from the group consisting of hyaluronic acid and a base metal salts of hyaluronic acid.

26. The pharmaceutical formulation for nasal administration according to any one of the claims from 17 to 25, wherein the base metal salt is a sodium or potassium salt.

27. The pharmaceutical formulation for nasal administration according to any one of the claims from 17 to 26, wherein the pharmacologically allowed additive is at least one compound selected from the group consisting of a preserving agent and an excipient.

28. The pharmaceutical formulation for nasal administration according to claim 27, wherein the pharmacologically acceptable additives contain the excipient and the preserving agent.

29. The pharmaceutical formulation for nasal administration according to claim 27 or 28, wherein the excipient is water.

30. The pharmaceutical formulation for nasal administration according to claim 27, 28 or 29 wherein the preserving agent is p-hydroxybenzoic acid ethyl ester.

31. The pharmaceutical formulation for nasal administration according to any one of the preceding claims, which is dosed through nasal mucosa.

32. The pharmaceutical formulation for nasal administration according to any one of the claims, which has a pH in the range from 6 to 8.

33. The pharmaceutical formulation for nasal administration according to claim 32, which has a pH in the range from 6.5 to 7.5.

34. A method for producing a pharmaceutical formulation for nasal administration which contains at least one pharmaceutically active polypeptide, the method comprising the steps of;

adding an adequate amount of distilled water to a compound selected from the group consisting of taurine, an ester thereof with C1~6 alcohol, a base metal salt of taurine, hyaluronic acid, a base metal salt of the hyaluronic acid, and a mixture thereof and an optional additive to form solution of the ingredients;

adjusting the pH of the solution formed by dissolving the compounds; and

adding a pharmaceutically active polypeptide to the solution and dissolving the pharmaceutically active polypeptide.

35. The method for producing the pharmaceutical formulation according to claim 34, which further includes the steps of;

filtering the solution for sterilization thereof; and

filling a bottle with the filtrate.

36. The method for producing the pharmaceutical formulation according to claim 34 or 35, wherein the pharmaceutically active polypeptide is selected from the group consisting of natural insulin, synthetic insulin, insulin produced from recombinant DNA, calcitonin, hirudin, glucagon, angiotensin, a lactation hormone, a growth hormone, a thyroid-stimulating hormone or thyrotropin, adrenocorticotropin, and inerferon and a mixture thereof.

37. The method for producing the pharmaceutical formulation according to claim 34, 35 or 36, wherein the additive is selected from the group consisting of a pharmacologically acceptable excipient and a pharmaceutically acceptable preserving agent, and a mixture thereof.

38. The method for producing the pharmaceutical formulation according to claim 34, 35, 36 or 37, wherein the pH of the solution is between 6 and 8.

39. The method for producing the pharmaceutical formulation according to claim 34, 35, 36, 37 or 38, wherein the pH of the solution is between 6.5 and 7.5.

40. The method for producing the pharmaceutical formulation according to any one of the claims from 34 to 39, wherein the pharmaceutical formulation is used for therapeutics for diabetes.

41. The method for producing the pharmaceutical formulation according to any one of the claims from 34 to 40, wherein the pharmaceutical formulation contains at least insulin, taurine and hyaluronic acid.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/JP 99/01704

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K47/20 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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P,X	WO 98 43664 A (LG CHEMICAL LIMITED ;KIM MYUNG JIN (KR); KIM SUN JIN (KR); KWON OH) 8 October 1998 see page 5, line 17 - line 20 see page 6, line 32 see page 7, line 4 - line 10 see claims 1,4,5,11; examples --- -/--	1,4-6,8, 10-13, 15-17, 20,22, 24, 26-29, 31-40

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 June 1999	25/06/1999

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2

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/JP 99/01704

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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2

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